

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/IN2005/000127

International filing date (day/month/year)
25.04.2005

Priority date (day/month/year)
01.07.2004

International Patent Classification (IPC) or both national classification and IPC
C07D277B2

Applicant
ALEMBIC LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No. .
PCT/IN2005/000127

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/N2005/000127

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 31,32

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 31,32 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form

- ☐ has not been furnished
- ☐ does not comply with the standard

- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IN2005/000127

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-30
	No: Claims	
Inventive step (IS)	Yes: Claims	1-30
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-30
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/IN2005/000127

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 31 and 32 do not contain any technical features and are thus so unclear (Art. 6 PCT) that no meaningful opinion can be given.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V-1. State of the art:

The following documents have been cited:

- D1: US-A-4 886 812 (GRISS, DECEASED ET AL) 12 December 1989 (1989-12-12) cited in the application
- D2: SCHNEIDER C S ET AL: "Dopamine autoreceptor agonists: resolution and pharmacological activity of 2,6-diaminotetrahydrobenzothiazole and aminothiazole analogue of apomorphine" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 30, no. 3, March 1987 (1987-03), pages 494-498, XP002186199 ISSN: 0022-2623 cited in the application
- D3: WO 2004/041797 A (CIPLA LTD; RAO, DHARMARAJ, RAMACHANDRA; KANKAN, RAJENDRA, NARAYANRAO;) 21 May 2004 (2004-05-21)

In the following paragraphs references to the above documents relate to the parts indicated in the search report unless specified otherwise.

V-2. Novelty (Art. 33(2) PCT)

Steps (a)-(e) of the process claimed in claims 1/2 as well as steps (g)/(h) of claim 2 are in principle known from D1, step (f) of claims 1/2 from D2.

The claimed processes are nevertheless novel over the cited documents on account of the use of a Lewis acid catalyst in step (c) and the use of a base in step (e).

The claims fulfil thus Art. 33(2) PCT.

V-3. Inventive step (Art. 33(3) PCT)

The application claims a multistep process for the preparation of pramipexole (I) and the key intermediate (II).

The process steps (a)-(e) of claim 1 are known from D1 and the final resolution of the racemate from D2.

The problem to be solved was the provision of an improved process to prepare these compounds.

The claimed solution lies in the modification of the process known from D1, i. e. the use of a Lewis acid catalyst in step (c) and the use of a base in step (e).

It appears from a comparison of present examples 4 and 5 with the respective steps in D1 (cf. steps (c) and (d) of example 2 there) that in fact the yields have been significantly improved. It might have to be clarified later on whether this improvement is credible for the claimed generalisations ("Lewis acid", "base" with respect to AlCl_3 , triethylamine).

The prior art does not contain hints which could have lead the skilled man to add a Lewis acid catalyst in the bromination of the cyclohexanone and to add a base in the hydrazinolysis of the phthalimide group to improve the yield.

The claims are thus considered to fulfil Art. 33(3) PCT.

Re Item VIII

Certain observations on the international application

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/IN2005/000127

- VIII-1. Claim 1 fails to define the structural formula II.
- VIII-2. Claim 2 contains all features of claim 1 and should thus be drafted as a dependent claim (cf. Rule 6.4(a) PCT).